REMARKS

Paragraph numbers herein refer to the Substitute Specification (clean copy) submitted on April 3, 2008.

Claims 1–16, 18 and 20–31 are pending in the present application. Claims 17 and 19 were canceled by an earlier amendment. Claims 26–31 are added by the present amendment.

Claims 14–16 are amended for enhanced clarity by reciting in each case a structural limitation, namely the amount of rotigotine present in the TTS effective to provide the specified result.

New Claims 26–28 are drawn to a TTS containing rotigotine in an amount effective for treatment of a disease associated with a dopamine-metabolism disorder (Claim 26), for example Parkinson's disease (Claim 27) or restless leg syndrome (Claim 28). Support for a "therapeutically effective" amount of rotigotine is found in the specification as filed, for example at p. 17, last paragraph; and support for the recited diseases is found in the specification as filed, at least at p. 21, first paragraph.

New Claims 29–31 are drawn to a method for treating a disease associated with a dopamine-metabolism disorder (Claim 29), for example Parkinson's disease (Claim 30) or restless leg syndrome (Claim 31), comprising applying a TTS of Claim 1 to skin of a patient in need thereof. Support for such a method is found in the specification as filed, for example at p. 21, second paragraph.

No new matter is added, and no change in inventorship is believed to occur, as a result of any amendment herein.

RESPONSE TO OFFICE ACTION DATED MARCH 19, 2009

1. Obviousness-type double patenting

Claims 1–16, 18 and 20–25 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 28–59 of copending application Serial No. 10/523,908.

The rejection is provisional because the allegedly conflicting claims have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be

otherwise allowable and/or once the co-pending application issues as a patent.

2. Rejection under 35 U.S.C. §103(a) over Chen in view of Metman and Loper

Claims 1–3, 6–16, 18 and 20–25 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,807,570 ("Chen"), in view of Metman *et al.* (2001) Clinical Neuropharmacology 24:163–169 ("Metman") and U.S. Patent No. 4,880,633 ("Loper"). This rejection is respectfully traversed.

2.1. Not all claimed features are taught or suggested by the cited art

The present claims are not obvious over the combination of Chen, Metman and Loper (even if motivation existed for such combination, which is not admitted herein), at least because the cited documents fail to teach or suggest all of the claimed features. To establish a *prima facie* case of obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); *In re Wilson*, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art").

In the case of independent Claim 1, the structure resulting from the process of dispersing, melting and partly or completely dissolving rotigotine in the hot-melt adhesive is absent from the cited art. In the case of Claim 18, the cited documents fail to teach or suggest melting and homogenizing components of the cement matrix including the active agent, solvent-free. In the case of Claim 20, the cited documents fail to teach or suggest pre-melting and homogenizing components of the cement matrix, solvent-free, and introducing the active agent into the pre-melted matrix. Details and shortcomings of the Chen, Metman and Loper disclosures are presented in Applicant's submission dated December 22, 2008 and are further explained below.

Claim 1 and claims dependent therefrom

All the features of Claim 1 must be considered against the combination of Chen, Metman and Loper. In particular, the transdermal therapeutic system (TTS) of Claim 1 is formed using a process that imparts a structure unattainable by the cited references: "the cement matrix comprises a hot-meltable adhesive in which the active substance is dispersed and melted using a hot-melt process," the active substance being rotigotine. As claimed, the

rotigotine is melted, whereas nowhere in the combination of Chen, Metman, and Loper is there any disclosure or suggestion with respect to melting an active substance.

Structure implied by processing should be considered when assessing the patentability of product-by-process claims over the art where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, for example, *In re Garnero*, 412 F.2d 276, 162 USPQ 221 (CCPA 1979), holding "interbonded by interfusion" to limit structure of the claimed composite and noting that terms such as "welded", "intermixed", "ground in place", "press fitted" and "etched" are capable of construction as structural limitations. In the present case, a "cement matrix compris[ing] a hot-meltable adhesive in which the active substance is dispersed and melted using a hot-melt process" makes the presently claimed TTS structurally distinguishable from anything found in Chen, Metman and Loper, as none of the cited documents teach or suggest melting the active substance. The "hot-melt deposition, extrusion and the like" of Loper employs a solution of drug and matrix material in a solvent, and removal of the solvent by drying (Loper, col. 8, lines 21–23). As the drug is in solution in a solvent, it cannot be said to be "melted". Furthermore, no indication is given by Loper that "hot-melt deposition, extrusion and the like" is carried out at a temperature above the melting point of the drug, which would presumably have to be lower than the boiling point of the solvent employed in Loper.

Applicant submits that dispersion of melted rotigotine in melted adhesive, per Claim 1, blends two molten materials resulting in a matrix that is structurally distinct from one derived by dissolving a drug in solvent and removing the solvent by drying, which is Loper's contribution to the present combination. As evidence, Applicant refers the Examiner to paragraph **[0008]** of the present specification, which illustrates drawbacks of solvent-based delivery systems. For example, at subparagraph (4) thereof:

> [A]s the solvent is removed during the production process, the relative concentration of the active substance increases, which can lead to an oversaturation of the matrix and to an undesirable formation of crystals. This again places a limit on the maximum amount of the active substance that can be worked into the matrix. Yet a low-level infusion of the active substance limits the release capacity of the matrix per unit of time and/or its functional lifespan due to a premature depletion of the active substance.

Therefore, the TTS of Claim 1 prepared by a hot-melt process is structurally distinct from a TTS prepared by a solvent process that might be derived from the cited art, wherein crystallization of the drug upon solvent removal would be expected.

The present specification further illustrates differences between solvent-based systems and hot-melt systems at paragraphs **[0059]–[0060]** thereof. For example, solvent-based systems using silicone adhesives can accept at the most 15% by weight rotigotine, whereas the adhesive matrices of hot-melt TTSs can accept significantly greater amounts of rotigotine, *e.g.*, up to 40% by weight. Loper's use of a solution of drug and matrix material, and removal of solvent by drying, would therefore limit the amount of active substance in comparison to the presently claimed TTSs made using a hot-melt process.

Since the combination of Chen, Metman and Loper fails to teach or suggest at least one feature of the present process (*i.e.*, melting rotigotine), the combination cannot produce the structure of the presently claimed TTS. Accordingly, Claim 1 and claims dependent therefrom (Claims 2–16 and new Claims 26–28 added by amendment herein) are not *prima facie* obvious over the cited art.

Claims 18 and 24

The present rejection fails to consider all the features of Claim 18 against the combination of Chen, Metman and Loper. In particular, Claim 18 recites "[a] method for preparing a TTS that comprises a rotigotine-containing cement matrix, the method comprising melting and homogenizing components of the cement matrix, solvent-free, in an extruder at a temperature between 70°C and 200°C prior to lamination of the components" (emphasis added). Hence, the claim expressly requires melting the rotigotine-containing cement matrix, contrary to the assertion in the Action at p. 7, lines 1–2.

Applicant respectfully submits that the Examiner's mischaracterization of Claim 18 as not requiring melting of the active agent voids the present rejection, as the combination of Chen, Metman and Loper fails to teach or disclose melting the active agent. Moreover, Claim 18 expressly recites that the components of the cement matrix are melted and homogenized solvent-free.

For at least these reasons, Claim 18 and Claim 24 dependent thereon are not *prima facie* obvious over the cited art.

Claims 20–23 and 25

With respect to Claim 20, the combination of Chen, Metman and Loper lacks any disclosure relating to "pre-melting and homogenizing components of the cement matrix other than the rotigotine, solvent-free, and introducing rotigotine at a temperature between 70°C and 200°C, into the pre-melted cement matrix" (emphasis added). In a process according to Claim 20, the cement matrix components are pre-melted and rotigotine is introduced thereafter. The process provided by Loper (*e.g.*, "hot-melt deposition, extrusion and the like") is silent with respect to any such details. Nowhere in the collective disclosures of Chen, Metman and Loper is the "reservoir matrix material" pre-melted then mixed with drug. For example, the limit of Loper's contribution is that "[a] solution of drug and reservoir matrix material is coated onto an impermeable backing ... [and] solvent is removed ... . The reservoir matrix may be coated onto the backing material using other techniques such [as] hot melt deposition, extrusion and the like ..." (Loper, col. 8, lines 20–29). Nothing indicates any pre-melting occurs in the reference combination. Likewise, the present claims expressly require pre-melting and homogenizing components solvent-free, which precludes any collective solvent-based process based on the combination of Chen, Metman, and Loper. Claim 20 and Claims 21–23 and 25 dependent thereon are consequently not *prima facie* obvious over the cited art.

2.2. No rationale to modify the cited art to include the missing subject matter

Where the combined references are missing claimed features, a case of obviousness requires an apparent reason, based either on the references themselves or on the general knowledge in the art, by which a skilled artisan would modify the references to include the missing subject matter. See *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (obviousness includes determining whether there was an apparent reason to combine known elements in the fashion claimed). With respect to the present claims, the references are devoid of any suggestion or appreciation of the benefits associated with melting the rotigotine and cement matrix (Claims 1 and 18), introducing rotigotine into a pre-melted

cement matrix (Claim 20), or using a solvent-free process (Claims 18 and 20). The present Action fails to provide any basis for a skilled artisan to forgo such use of solvent or include the present melting or pre-melting processes, as required by *In re Kahn*, 441 F3d 977, 78 USPQ2d 1329 (Fed. Cir. 2006) ("rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning to support the legal conclusion of obviousness"). In contradistinction, the present disclosure illustrates several advantages and benefits over solvent-based systems (see specification, paragraph **[0008]**. Absent the articulated reasoning required by *In re Kahn* and by *KSR*, the combination of Chen, Metman and Loper cannot support a *prima facie* case of obviousness.

2.3. Predictability of outcome required for *prima facie* obviousness is lacking

In addition, Applicant reiterates that it could not have been predicted that rotigotine would lend itself to processing by the present hot-melt methods in that it remains stable under short-term heating to temperatures up to at least 160°C, and further, it could not have been predicted that rotigotine would be released from matrices prepared in this way in a continuous fashion and at a therapeutically desirable rate (specification, paragraph **[0026]**). Although rotigotine is known to be susceptible to oxidation, it remains stable on melting and is present in the resulting matrix at a purity level that is routinely better than 98% and generally over 99%, as measured at 220 nm and 272 nm by HPLC (specification, paragraph **[0027]** and Tables 2, 3 and 4). The present compositions can include higher rotigotine concentrations than are possible in compositions prepared by solvent-based processes; furthermore, the present invention provides improved safety and processing times (specification, paragraph **[0030]**).

None of these outcomes was predictable from the combined disclosure of Chen, Metman and Loper. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art (MPEP 2143.01.III, citing *KSR*, *supra*). For at least this reason, the present claims are not *prima facie* obvious over the cited art.

2.4. Rejection over Chen in view of Metman and Loper: conclusion

Independent Claims 1, 18 and 20, and all claims dependent directly or ultimately

therefrom, are for reasons set forth above not obvious over the cited art. Withdrawal of the present 35 U.S.C. §103(a) rejection over Chen in view of Metman and Loper is respectfully requested.

3. Rejection under 35 U.S.C. §103(a) over Chen in view of Metman, Loper and Noel

Claims 1–16, 18 and 20–25 are rejected under 35 U.S.C. §103(a) as allegedly obvious over Chen in view of Metman, Loper and U.S. Patent No. RE 36,754 ("Noel"). This rejection is respectfully traversed.

The combination of the Chen, Metman, Loper and Noel documents cannot establish a *prima facie* case of obviousness for independent Claims 1, 18 and 20 since in each case the combination is missing one or more of the claimed features. The failure of a three-way combination of Chen, Metman and Loper to establish *prima facie* obviousness of the present claims is demonstrated above. Addition of Noel fails to cure the shortcomings of the three-way combination of Chen, Metman and Loper, and, what is more, the Chen and Noel disclosures are incompatible and cannot be properly combined as no reason is provided as to how a skilled artisan would reconcile their disparate teachings.

Details of the Noel art are presented in Applicant's submission dated December 22, 2008 and are further explained below.

Chen in view of Metman, Loper and Noel, fails to teach or suggest a method, or product made by such method, in which rotigotine as active substance is dispersed and melted using the claimed hot-melt process. In particular, the combination of documents cited in the present rejection fails to teach or suggest infusing or dispersing any active substance, rotigotine or otherwise, wherein the active substance is melted. Thus, even if a skilled artisan attempted to combine the various disclosures of Chen, Metman, Loper and Noel (no admission is made herein that motivation would have existed for such combination), the combination would not provide all the features of the present claims.

The combination also fails to provide an apparent rationale by which a skilled artisan would modify the collective teachings to include the missing subject matter, and no reason based on the general knowledge in the art is identified by which a skilled artisan would be led to include the missing subject matter.

In addition, Chen's use of ropinirole dissolved in water or other solvent and mixed with a polymer to form a reservoir layer is at odds with Noel's preference for using a solvent-free composition and the benefits attributed by Noel to the hot-melt silicone system. It is not clear how a person of ordinary skill would reconcile these disparate teachings without contravening the operation of one of these references. Only the present specification and claims appreciate the surprising result that rotigotine remains stable in admixture with molten adhesive after the drug is melted (specification, paragraph **[0108]**).

Independent Claims 1, 18 and 20, and all claims dependent directly or ultimately therefrom, are for reasons set forth above not obvious over the cited art. Withdrawal of the present 35 U.S.C. §103(a) rejection over Chen in view of Metman, Loper and Noel is respectfully requested.

4. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,
HARNESS, DICKEY & PIERCE, P.L.C.

James C. Forbes
Agent for Applicant
Reg. No. 39,457
Tel. 847-412-6350